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## Fax Cover Sheet

| | | | |
|---|---|---|---|
| **Date:** | Monday, July 9, 2007 | **Time:** | 1:17 PM |
| **To:** | Commissioner for Patents<br>United States Patent and Trademark Office | **Phone:** | none |
| | | **Fax:** | 1-571-273-8300 |
| **From:** | Gary R. Fabian<br>Registration No. 33,875 | **Phone/Fax:** | (650) 780-9030 |
| **Re:** | U.S. Patent Application Serial No. 10/669,768 | (Onyx Ref. ONYX1047.DIV) | |

**Number Of Pages Including Cover Sheet:** 70 ( Seventy pages)

## Message

THE ATTACHED DOCUMENTS ARE TO BE MADE OF OFFICIAL RECORD

Transmitted herewith for filing in the above-referenced application are the following documents:

1. Transmittal Letter
2. Petition to the Director of Technology Center 1600 under 37 C.F.R. § 1.181 Regarding an Improper Action by the Examiner in *Ex Parte* Prosecution, including Exhibits A, B, C, and D; and
3. Certificates of Facsimile Transmission.

Onyx Dkt No. ONYX1047.DIV
USSN: 10/669,768
PATENT

**CERTIFICATE OF TRANSMISSION BY FACSIMILE (37 CFR 1.8)**
I hereby certify that this correspondence is being facsimile transmitted to the Commissioner for Patents, United States Patent and Trademark Office, (Fax No. 571-273-8300) on the date indicated.

Gary R Tobin — Signature
9 July 2007 — Date of Transmittal

| IN THE UNITED STATES PATENT AND TRADEMARK OFFICE | |
|---|---|
| In Re Application of: Shen, Y., et al. | Confirmation No. 8135 |
| Serial No.: 10/669,768 | Art Unit: 1633 |
| Filing Date: 24 September 2003 | Examiner: M. Marvich |
| Title: ADENOVIRUS E1B-55K SINGLE AMINO ACID MUTANTS AND METHODS OF USE | |

## TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing in the above-referenced application are the following documents:

1. Transmittal (in duplicate);
2. Petition to the Director of Technology Center 1600 under 37 C.F.R. § 1.181 Regarding an Improper Action by the Examiner in *Ex Parte* Prosecution, including Exhibits A, B, C, and D; and
3. Certificates of Transmission by Facsimile.

**Authorization to Charge Deposit Account**: No additional fees are believed due in connection with this paper. However, the Commissioner is hereby authorized to charge to Deposit Account No. 15-0615 (please reference ONYX 1047.DIV) any fees required for the Petition to the

Director of Technology Center 1600 under 37 C.F.R. § 1.181 or any fees required by this paper under 37 C.F.R. §§ 1.16, 1.17 and 1.21, with the exception of the payment of the Issue Fee.

Respectfully submitted,

Dated: 9 July 2007

By : Gary R. Fabian

Gary R. Fabian, Ph.D.
Registration No. 33,875
Agent for Applicants

ONYX Pharmaceuticals, Inc.
2100 Powell Street
Emeryville, CA 94608
Phone: (510) 597-6502
Facsimile: (510) 597-6610

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JUL 0 9 2007



**CERTIFICATE OF TRANSMISSION BY FACSIMILE (37 CFR 1.8)**
I hereby certify that this correspondence is being facsimile transmitted to the Commissioner for Patents, United States Patent and Trademark Office, (Fax No. 571-273-8300) on the date indicated.

Gary R Tabrizi — Signature
9 July 2007 — Date of Transmittal

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In Re Application of: Shen, Y., et al. | Confirmation No. 8135 |
| Serial No.: 10/669,768 | Art Unit: 1633 |
| Filing Date: 24 September 2003 | Examiner: M. Marvich |
| Title: ADENOVIRUS E1B-55K SINGLE AMINO ACID MUTANTS AND METHODS OF USE | |

## TRANSMITTAL



Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith for filing in the above-referenced application are the following documents:

1. Transmittal (in duplicate);
2. Petition to the Director of Technology Center 1600 under 37 C.F.R. § 1.181 Regarding an Improper Action by the Examiner in *Ex Parte* Prosecution, including Exhibits A, B, C, and D; and
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Respectfully submitted,

Dated: 9 July 2007

By : Gary R Fabian

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Onyx Dkt No. ONYX1047.DIV
USSN: 10/669,768
PATENT

CERTIFICATE OF TRANSMISSION BY FACSIMILE (37 C.F.R. 1.8)
I hereby certify that this correspondence is being facsimile transmitted to the Commissioner for Patents, United States Patent and Trademark Office, (Fax No. 571-273-8300) on the date indicated.

Gary R. Faber — 9 July 2007
Signature — Date of Transmittal

| IN THE UNITED STATES PATENT AND TRADEMARK OFFICE | |
|---|---|
| In Re Application of: Shen, Y., et al. | Confirmation No. 8135 |
| Serial No.: 10/669,768 | Art Unit: 1633 |
| Filing Date: 24 September 2003 | Examiner: M. Marvich |
| Title: ADENOVIRUS E1B-55K SINGLE AMINO ACID MUTANTS AND METHODS OF USE | |

**Petition to the Director of Technology Center 1600 under 37 C.F.R. § 1.181 Regarding an Improper Action by the Examiner in *Ex Parte* Prosecution**

George C. Elliot
Director of Technology Center 1600
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a petition to invoke the supervisory authority of the Director of the USPTO Technology Center 1600 under 37 C.F.R. §1.181 in an *ex parte* action or requirement in a patent application by the Examiner which is not subject to appeal (37 C.F.R. §1.191) and not otherwise provided for (*See* M.P.E.P. § 1002.02(c)), specifically regarding the Examiner's action of rejection of previously allowed claims.

According to M.P.E.P. §706.04, Rejection of Previously Allowed Claims (emphasis added):

> A claim noted as allowable shall thereafter be rejected only after the proposed rejection has been submitted to the primary examiner for consideration of all the facts and approval of the proposed action.

> **Great care should be exercised in authorizing such a rejection.** See Ex parte Grier, 1923 C.D. 27, 309 O.G. 223 (Comm'r Pat. 1923); Ex parte Hay, 1909 C.D. 18, 139 O.G. 197 (Comm'r Pat. 1909).

The above-referenced application is still pending.

The present petition is filed within TWO-MONTHS of the mailing date of the Office action from which relief is requested (see, 37 C.F.R. §1.181(f)).

For the following reasons, applicants submit that "great care" has not been exercised in authorizing the rejection of applicants' previously allowed claims. In particular, the newly asserted scope rejection is a reinstatement of a previously overcome scope rejection.

**Statement of Facts (37 C.F.R. §1.181(b)):**

**1. Claims 11-13, and 24-28 were twice indicated as allowable with inclusion of the limitation of claim 12.** In the Office action, mailed 19 June 2006 (*See* Exhibit A), the Examiner stated:

> Claim 12 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claim. (Office action, mailed 19 June 2006, page 10).

In response to the Office action, applicants amended independent claim 11, from which claim 12 originally depended, to include the limitation presented in claim 12 (*See* Response and Amendment, mailed 19 September 2006). In response to applicants' amendment, the Examiner indicated that claims 11-13, 24-28, and 34 were ALLOWED (*See* final Office action, dated 14 December 2006, page 10, Exhibit B).

Accordingly, claims 11-13, 24-28, and 34 were indicated as ALLOWED.

**2. Claim 34 was indicated as allowable.** In the final Office action, mailed 14 December 2006, the Examiner indicated that claims 11-13, 24-28, and 34 were ALLOWED (*See* final Office action, dated 14 December 2006, page 10, Exhibit B). Claim 34 was dependent on independent claim 33. In response to the final Office action, applicants amended independent claim 33 to include the limitation present in independent claim 34 (*See* Response to Final Rejection and Amendment, filed 16 April 2007) and cancelled two other groups of claims rejected by the Examiner (*See* 37 C.F.R. §1.116 Amendments and affidavits

or other evidence after final action and prior to appeal -- "(1) An amendment may be made canceling claims or complying with any requirement of form expressly set forth in a previous Office action.").

Independent claims 11 and 33 comprise essentially the same limitations with the exception that claim 33 is limited to "administering by direct injection into the tumor a dose of a recombinant adenovirus." The limitations of the claims dependent on claims 11 and 33 correspond as follows: (claims dependent on claim 11) 13, 25, 26, 27, 28 and 24; and (claims dependent on claim 33) 35, 36, 37, 38, 39 and 40, respectively. Thus, based on (i) the indication by the Examiner that the limitation present in claim 34 rendered the independent claim allowable, and (ii) the correspondence of the claim limitations between the claims dependent on claim 33 and the claims dependent on claim 11, applicants submit that the amendment of claim 33 to include the limitation of claim 34 rendered claim 33 and its dependent claims allowable.

Accordingly, after applicants' response to the final rejection, claims 11-13, 24-28, 33, and 35-40 were in condition for allowance.

**3. The "new rejection" asserted by the Examiner is not new and was previously overcome.** In response to applicants' Response to Final Rejection and Amendment, filed 16 April 2007, the Examiner issued a "new", non-final Office action (mailed 9 May 2007, Exhibit C). Most importantly, the non-final Office action, mailed 9 May 2007, **IS NOT A NEW REJECTION, IT CORRESPONDS TO A PREVIOUSLY PRESENTED REJECTION, AND THE PREVIOUSLY PRESENTED REJECTION WAS WITHDRAWN BY THE EXAMINER.**

In the non-final Office action, mailed 9 May 2007 (Exhibit C), the Examiner asserts a scope rejection of claims 11, 12, 24, 28, 33, 39 and 40 under 35 U.S.C. §112, first paragraph, asserting that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims. The arguments and analysis set forth in this "new" rejection are essentially duplicative of the arguments set forth in the Examiner's previous rejection of the claims under 35 U.S.C. §112, first paragraph, in the Office action, mailed 19 June 2006, with the following minor exceptions:

(a) sections 1-4 of the rejection match essentially word for word;

(b) section 4 of the "new" rejection has been changed to incorporate material previously presented in section 5 of the rejection mailed 19 June 2006. The moved material corresponds to the discussion of the Kirn, et al. reference; and

(c) the first paragraph of section 5 of the "new" rejection corresponds essentially to the paragraph spanning pages 8-9 of section 5 of the rejection mailed 19 June 2006 (e.g., "by recitation that the rAd comprises an E1B-55K mutation, the adenovirus to be used in the treatment encompasses a broad and diverse genus of adenovirus that need only be linked by a mutation in the E1B-55K" compare, page 8, line 20, to page 9, line 1, Office action, mailed 19 June 2006 (Exhibit A), and page 4, line 20, to page 5, line 1 of the "new" rejection (Exhibit C)). The last paragraph of section 5 of the "new" rejection essentially consists of unsubstantiated assertions by the Examiner that applicants have failed to teach one of ordinary skill in the art how to make and use the invention commensurate in scope with the claims (this aspect is discussed further herein below in part 5 of this petition).

In applicants' Response and Amendment, mailed 19 September 2006, applicants briefly argued the Examiner's rejection, but, in an effort to facilitate prosecution, amended the claims to include the limitation of claim 12 into independent claim 11, from which claim 12 originally depended, to include the limitation presented in claim 12 (*See* Response and Amendment, mailed 19 September 2006). In response to applicants' amendment, the scope rejection of claims 11, 13 and 24-28 under 35 U.S.C. §112, first paragraph, was withdrawn and the Examiner indicated that claims 11-13, 24-28, and 34 were ALLOWED (*See* final Office action, dated 14 December 2006, page 10 (Exhibit B)).

As discussed herein above, in response to the Examiner's final rejection of the remaining claims, applicants cancelled two groups of claims and amended claims 33, and 35-40 to conform to the limitations present in allowed claims 11-13 and 24-28.

Accordingly, the Examiner's reinstatement of the previously overcome scope rejection of, at least, claims 11-13, 24-28, and 34 in the non-final Office action following the final Office action is completely improper.

**4. The Examiner's "new" rejection under 35 U.S.C. §112, first paragraph, provides no new evidence to support the Examiner's position.**

As stated by MPEP 706.07(e) Withdrawal of Final Rejection:

> Although it is permissible to withdraw a final rejection for the purpose of entering a new ground of rejection, this practice is to be limited to situations where a new reference either fully meets at least one claim or meets it except for differences which are shown to be completely obvious. Normally, the previous rejection should be withdrawn with respect to the claim or claims involved.

In the present situation, no new art is being applied nor has any new evidence been presented by the Examiner. The "new" rejection under 35 U.S.C. §112, first paragraph, is a reinstatement of a previous scope rejection which was overcome during prosecution by applicants' amendment.

Accordingly, issuance of a new, non-final Office action after the final Office action was improper.

**5. The Examiner's "new" rejection under 35 U.S.C. §112, first paragraph, contains only unsubstantiated assertions and is contradicted by the teachings of the specification.**

The Examiner's assertion that applicants have failed to teach a person skilled in the art to make and use the invention commensurate in scope with the claims is unsubstantiated and contradicted by the teachings of the specification. For example, in the "new" rejection of the claims under 35 U.S.C. §112, first paragraph, the Examiner states that "applicants have not provided the structural requirements of the single amino acid mutants such that one of skill in the art would be able to identify those mutants that have lost the ability to bind efficiently to p53" (Office action, mailed 9 May 2007, page 5 (Exhibit C)).

On the contrary, as noted by the Examiner the specification teaches the construction of 26 mutants in the E1B-55K coding region and further provides to one having ordinary skill in the art extensive teachings regarding how to construct such mutants in the E1B-55K coding region (see, for example, Example 1, **Construction of E1B-55K Mutant Viruses**, pages 17-19 of the specification, corresponding to page 8, col. 2, to page 9 col. 1 of the published U.S. Patent Application No. US 2005/0053581 (Exhibit D)). Accordingly,

applicants have taught how to make the mutants of the present invention.

Further, applicants teach one of ordinary skill in the art how to identify (i.e., use) those mutants that have lost the ability to bind efficiently to p53 (see, for example, Example 2, **Binding of E1B-55K Mutants with p53** and E4orf 6, pages 19-22 of the specification, corresponding to page 10, col. 1, to page 11, col. 2 of the published U.S. Patent Application No. US 2005/0053581 (Exhibit D)). In particular, applicants teach a Western blotting analysis that identified adenoviral mutants that fail to bind to p53 (see, for example, ¶ 0092-¶ 0094 of the published U.S. Patent Application No. US 2005/0053581), as well as immunoprecipitation experiments to confirm the failure of the adenoviral mutants to bind to p53 (see, for example, ¶ 0095-¶0096 of the published U.S. Patent Application No. US 2005/0053581).

Applicants have taught one of ordinary skill in the art how to make and use the claimed adenovirus mutants of the present invention. Accordingly, the Examiner has failed to provide any evidentiary basis to reinstate the scope rejection of the claims under 35 U.S.C. §112, first paragraph. Again, the "new" scope rejection of the claims is completely improper.

**Action Requested (37 C.F.R. §1.181(b)):**

Applicants request withdrawal of the "new", non-final rejection and issuance of a Notice of Allowability for the pending claims, i.e., claims 11-13, 24-28, 33, and 35-40.

**Authorization to Charge Deposit Account:**

No fees are believed due; however, an authorization to charge any required fee for this petition to Deposit Account No. 15-0615 (please reference **ONYX1047.DIV**) accompanies this paper in the Transmittal Letter (provided in duplicate).

Respectfully submitted,

Date: 9 July 2007 By: Gary R Fabian

Gary R. Fabian, Ph.D.
Registration No. 33,875
Agent for Applicants

**Exhibit A**

**Office action, mailed 19 June 2006**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/669,768 | 09/24/2003 | Yuqiao Shen | ONYX1047-DIV | 8135 |

37499 7590 06/19/2006

ONYX PHARMACEUITICALS, INC.
2100 POWELL STREET
12TH FLOOR
EMERYVILLE, CA 94608

| EXAMINER | |
|---|---|
| MARVICH, MARIA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

DATE MAILED: 06/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) |
|---|---|---|
| | 10/869,768 | SHEN ET AL. |
| | Examiner | Art Unit |
| | Maria B. Marvich, PhD | 1633 |



*– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11-19 and 23-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 13-19 and 23-32* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This office action is in response to a response to a restriction requirement filed 4/5/06. Claims 1-10 and 20-22 have been cancelled. Claims 23-32 have been added. Claims 11-19 have been amended. Claims 11-19 and 23-32 are pending in the application.

### *Election/Restrictions*

Applicant's election with traverse of Group V in the reply filed on 4/5/06 is acknowledged. The traversal is on the ground(s) that claim 11 and 14 represent a genus of claims drawn to rAd comprising mutated E1B-55K proteins comprising a single amino-acid mutation. The viruses have previously been found allowable. Upon reconsideration Groups V and VI have been rejoined. Therefore, claims 11-19 and 23-32 are under examination in this office action.

### *Priority*

In the reference to the prior application inserted, as the first sentence of the specification of this application, the current status of all nonprovisional parent applications referenced should be updated. Specifically, U.S. Serial No. 09/918,696, filed 7/30/01, is now U.S. Patent No. 6, 635244, which is not indicated in the priority statement.

***Oath/Declaration***

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the signatures of the inventors are so light that they are not legible.

***Information Disclosure Statement***

An IDS filed 4/5/06 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

***Drawings***

Figure 3 is objected to under 37 CFR 1.83(a) because it fail to show any details as described in the specification. Specifically, figure 3 is a photograph of immunofluorescent cells. However, the details are indiscernible as the image is too dark. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

***Claim Objections***

Claims 11 and 14 are objected to because of the following informalities: the claim recites that the ability of an E1B-55K mutated protein to bind to p53 is reduced when compared to the wild-type E1b-055K protein. For grammatical accuracy, it would be remedial to recite "when compared to the ability of wild-type E1B-55K protein to bind to p53".

Claim 11 is objected to for recitation of "said E1B-55K mutated protein", for accuracy, it would be remedial to recite -- said mutated E1B-55K protein --.

As well, claims 11 and 14 are objected to ass recitation of "said treatment" should be -- the treatment -- for accuracy.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-19, 23 and 29-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation that the patient is administered "a polynucleotide sequence encoding a recombinant adenovirus" has been added to claim 14 and that the polynucleotide is RNA has

been added to claim 15. Applicant has indicated that support for this limitation is found throughout the specification as well as original claim 1. However, the examiner has been unable to find literal support in the originally filed specification or claims for the administration of "a polynucleotide sequence encoding a recombinant adenovirus". The specification does not contemplate administration of the polynucleotide encoding rAd for treatment but teaches infection of patients for delivery of the rAd. Therefore, the limitation is impermissible NEW MATTER.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 13-19 and 23-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of cancer characterized by p53 loss or deficiency by direct administration of a replication competent rAd to a tumor, does not reasonably provide enablement for treating any type of cancer in a human using a recombinant adenovirus comprising a single amino acid mutation in the E1B-55K gene and any other embodiments than replication competent using any other embodiments of administration than direct administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention.** The instant invention is drawn to recombinant adenovirus comprising single amino acid mutations in the E1B-55K gene such that binding to p53 is reduced as compared to binding between p53 and wild-type E1B-55K. The invention utilizes disciplines of molecular biology, virology and clinical technology.

2) **Scope of the invention.** Applicants' claims are broadly drawn to treatment of any cancer using recombinant adenovirus comprising any mutation in E1B-55K in which the adenovirus comprises a single amino acid mutation in E1B-55K such that binding to p53 is reduced. Applicants' disclosure teaches development of two such mutants in which amino acid 240 and 260 are mutated to generate Onyx 051 and Onyx 053. These mutants are not able to bind to p53. As described in the specification, the method of the instant invention is directed toward treating cancer using the vectors and is based upon oncolytic replication function of the viruses in infected tumor cells.

3) **Number of working examples and guidance.** The instant invention is drawn to single amino acid mutations within E1B-55k that affect binding to p53. Applicants have constructed 26 mutant rAd in which a single amino acid within the E1B-55K coding sequence

was mutated (see e.g. page 12, ¶ 4 and table 2). Two of these mutant R240A and H260A lost ability to bind p53 but did not lose late viral function. Furthermore, the cells were tested for oncolytic affect. U20S and Du145 cells were assayed and demonstrated that the two viruses were cytotoxic.

4) **State of Art.** Enormous efforts have been directed toward the development of vectors for cancer treatments. Each goal alone is complex and requires great skill in the art. Adenovirus mutants that lack the ability to bind to p53 are replication deficient in non-replicating, non-neoplastic cells with p53 but in cells deficient in p53, the virus is replicative and oncolytic. Previously, the art has described generation of rAd comprising deletions, substitutions and frame-shifts which inactivate the ability of E1B-55K to bind to p53 efficiently to generate E1B-p53- mutants. For example, ad2 dl1520 (Onyx 015) comprises a frame-shift mutation at nucleotide position 2022 that generates a stop codon 3 amino acids downstream of the AUG codon resulting in deletion of large region of E1B, US patent 5,677,178 describes the generation of rAd lacking E4orf6 and US 6,080,578 teaches construction of Onyx 019, 020 and 021 in which various amounts of internal sequences are deleted.

5) **Unpredictability of the art.** The enablement of the instant invention has been assessed in light of the specification and the prior art available at the time of filing. "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the

instant case, there are multiple inoperative embodiments when considering the use of the instant invention in humans such as 1) the claims recite broadly treatment of all cancers however, the efficacy of oncolytic viruses based upon E1B mutations has not been demonstrated to be efficacious against any type of cancer and 2) the lack of recited route of administration of the rAd exacerbate the unpredictability of the art. In light of the art at the time of filing, the instant invention would require undue experimentation to perform the invention in humans.

The instant invention is unpredictable for treatment of cancer in humans for the following reasons. First, applicants' invention is based upon the premise that the targeted mutations within E1B-55K resulting a virus that is selective to tumor cells as tumor cells lack p53 while normal cells do not. The specification teaches that "Therapy of disease, preferably neoplastic disease, wherein the disease arises from loss of p53 or a defect in the p53 pathway, may be afforded by administering to a patient a composition comprising adenoviral E1B55K mutants of the invention." Kirn et al teach that "the role of p53 in replication-selectivity of dl1520 has been difficult to confirm despite extensive *in vitro* experimentation by many groups, E1B-55K gene deletion was associated with decreased replication and cytopathogenicity in p53(+) tumor cells versus matched p53(-) tumor cells, relative to wild-type in RKO and H1299 cells" (page 6653, col 1, ¶ 3). Therefore, the efficacy of the instant adenovirus lies in treatment of p53 (-) tumors. This efficacy has been specifically observed when in combination with chemotherapy (see Kirn et al, page 6666, col 1). Secondly, this premise is distinctly connected to the replicative condition of the rAd. However, by recitation that the rAd comprises an E1B-55K mutation, the adenovirus to be used in the treatment encompasses a broad and diverse genus of adenoviruses

that need only be linked by a mutation in E1B-55K. The nature of the adenoviruses for treatment of cancer according to the instant invention must be replicative.

Thirdly, the method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al (Verma and Somia, Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. Russell teaches "it should first be capable of gaining access to a sufficient number of tumour cells in the patient to bring about a desired therapeutic outcome. Reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle position in a tumour deposit." (page 1165, col 2, ¶ 4-5). In the instant case, the method of delivery of an Onyx based virus is problematic, intratumoral injection is the preferred route of administration as it limits the virus to target tissue due to its cytotoxicity Adenoviral vector use for gene therapy is hindered by the transient nature of the transgene expression coupled with host immune responses. Attempts through oncolytic viral therapy to capitalize on the cell-killing or cellular immune response are also thwarted by the humoral immune responses as taught by Verma and Somia; "Unfortunately for gene therapy, most of the human population will probably have antibodies to adenovirus from previous infection with the naturally occurring virus" (Verma and Somia, p 241). And "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less

desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene (p. 4, column 2).

6) **Summary**. The invention recites a method for treatment of cancer using a replicative adenovirus vector. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established protocols and the inability to predict successful administration of the rAd: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

***Conclusion***

Claims 11, 13-19 and 23-32 are rejected.

Claim 12 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1633

June 7, 2006

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

**Exhibit B**

**Final Office action, dated 14 December 2006**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/669,768 | 09/24/2003 | Yuqiao Shen | ONYX1047-DIV | 8135 |

37499 7590 12/14/2006

ONYX PHARMACEUITICALS, INC.
2100 POWELL STREET
12TH FLOOR
EMERYVILLE, CA 94608

| EXAMINER | |
|---|---|
| MARVICH, MARIA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

| APPLICATION NO./ CONTROL NO. | FILING DATE | FIRST NAMED INVENTOR / PATENT IN REEXAMINATION | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 10/669,768 | | | |

| EXAMINER | |
|---|---|
| ART UNIT | PAPER |
| | 20061205 |

DATE MAILED:

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner for Patents**

Drawings
The color photographs and/or color drawings have been received and satisfy the requirements set forth in 37 CFR 1.84(b)(2). The petition filed under 37 CFR 1.84(a)(2) is granted.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to whose telephone number is (571) 272-0774.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739.

Joe Woitach
AU 1633

JOSEPH WOITACH, PH.D.
PRIMARY EXAMINER

PTO-90C (Rev.04-03)

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/669,768 | SHEN ET AL. | |
| | Examiner | Art Unit | |
| | Maria B. Marvich, PhD | 1633 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *9/21/06*.

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *14,16,17,24-47 and 111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *11-13,24-28 and 34* is/are allowed.

6)☒ Claim(s) *14,16,17,29-33 and 35-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *90-c*.

## DETAILED ACTION

### *Response to Amendment*

Any rejection of record in the previous action not addressed in this office action is withdrawn.. There are no new grounds of rejection herein and therefore, this action is final.

### *Drawings*

Receipt of a color drawing in replacement of figure 3 is acknowledged. The drawings have been accepted see attached 90C.

### *Claim Rejections - 35 USC § 112, first paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 16, 17, 29-32 and 41-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action mailed 6/19/06 and restated below. The rejection has been slightly reworded based upon applicants' amendment. The rejection has been extended to newly added claims 41-47.**

The limitation that the patient is administered "a polynucleotide DNA sequence encoding a recombinant adenovirus" has been added to claim 14. Newly added claim 41 recites that a

patient in need of treatment is administered by direct injection isolated polynucleotide DNA sequence encoding a recombinant adenovirus. Applicant has indicated that support for this limitation is found throughout the specification as well as original claim 1. However, the examiner has been unable to find literal support in the originally filed specification or claims for the administration of "a polynucleotide sequence encoding a recombinant adenovirus". The specification does not contemplate administration of the polynucleotide encoding rAd for treatment but teaches infection of patients for delivery of the rAd. Therefore, the limitation is impermissible NEW MATTER.

***Response to Argument***

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph for new matter on pages 8-10 of the amendment filed 9/21/06. Applicants argue that support is found in the description of the invention for example on page 16, lines 14-17, which teaches that adenoviruses or the DNA contained therein may be delivered to the cells. Furthermore, applicants argue that they are in possession of the polynucleotide sequences.

Applicants' arguments filed 9/21/06 have been fully considered but they are not persuasive. Applicants claims are drawn to a method of treating neoplastic cancer by administration of the polynucleotide to the patient and in this recitation it is interpreted that the polynucleotide is not contained in the adenovirus as recited in the specification on page 16, liens 14-17 but is administered as DNA. While the specification teaches that the adenovirus with the DNA is administered, this does not support teachings that are directed to administration of the DNA to the subject. As to newly added claim 41, the specification teaches on page 15, line 13-

23, suspension of virion particles can be directly injected into the tumor mass. Again, while the DNA is contained in the adenovirus particles, this does not encompass conditions in which the DNA is injected independent of the adenovirus. As the specification does not set forth administration of the DNA separate form the polynucleotides, the limitation that the patient is administered "a polynucleotide DNA sequence encoding a recombinant adenovirus" is impermissible new matter.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 16, 17, 29-32, 32, 33 and 35-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of cancer characterized by p53 loss or deficiency by direct administration of a replication competent rAd to a tumor, does not reasonably provide enablement for treating any type of cancer in a human using a recombinant adenovirus comprising a single amino acid mutation in the E1B-55K gene and any other embodiments than replication competent using any other embodiments of administration than direct administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 6/19/06 and restated below. The rejection has been slightly**

**reworded based upon applicants' amendment. The rejection has been extended to newly added claims 33 and 35-47.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention.** The instant invention is drawn to recombinant adenovirus comprising single amino acid mutations in the E1B-55K gene such that binding to p53 is reduced as compared to binding between p53 and wild-type E1B-55K. The invention utilizes disciplines of molecular biology, virology and clinical technology.

2) **Scope of the invention.** Applicants' claims are broadly drawn to treatment using recombinant adenovirus comprising any mutation in E1B-55K in which the adenovirus comprises a single amino acid mutation in E1B-55K such that binding to p53 is reduced. Applicants' disclosure teaches development of two such mutants in which amino acid 240 and 260 are mutated to generate Onyx 051 and Onyx 053. These mutants are not able to bind to p53. As described in the specification, the method of the instant invention is directed toward treating cancer using the vectors and is based upon oncolytic replication function of the viruses in infected tumor cells.

3) **Number of working examples and guidance.** The instant invention is drawn to single amino acid mutations within E1B-55k that affect binding to p53. Applicants have constructed 26 mutant rAd in which a single amino acid within the E1B-55K coding sequence was mutated (see e.g. page 12, ¶ 4 and table 2). Two of these mutant R240A and H260A lost ability to bind p53 but did not lose late viral function. Furthermore, the cells were tested for oncolytic affect. U20S and Du145 cells were assayed and demonstrated that the two viruses were cytotoxic.

4) **State of Art.** Enormous efforts have been directed toward the development of vectors for cancer treatments. Each goal alone is complex and requires great skill in the art. Adenovirus mutants that lack the ability to bind to p53 are replication deficient in non-replicating, non-neoplastic cells with p53 but in cells deficient in p53, the virus is replicative and oncolytic. Previously, the art has described generation of rAd comprising deletions, substitutions and frame-shifts which inactivate the ability of E1B-55K to bind to p53 efficiently to generate E1B-p53- mutants. For example, ad2 dl1520 (Onyx 015) comprises a frame-shift mutation at nucleotide position 2022 that generates a stop codon 3 amino acids downstream of the AUG codon resulting in deletion of large region of E1B, US patent 5,677,178 describes the generation of rAd lacking E4orf6 and US 6,080,578 teaches construction of Onyx 019, 020 and 021 in which various amounts of internal sequences are deleted.

5) **Unpredictability of the art.** The enablement of the instant invention has been assessed in light of the specification and the prior art available at the time of filing. "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue

experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, there are multiple inoperative embodiments when considering the use of the instant invention in humans such as 1) the claims recite broadly that the virus is a recombinant adenovirus comprising any mutation in E1B, however, the efficacy of the virus is based upon its oncolytic activity and 2) the lack of recited route of administration of the rAd exacerbate the unpredictability of the art. In light of the art at the time of filing, the instant invention would require undue experimentation to perform the invention in humans.

The instant invention is unpredictable for treatment of cancer in humans for the following reasons. First, applicants' invention is based upon the premise that the targeted mutations within E1B-55K resulting a virus that is replicative in tumor cells lack p53 while normal cells do not. Kirn et al teach that "the role of p53 in replication-selectivity of dl1520 has been difficult to confirm despite extensive *in vitro* experimentation by many groups, E1B-55K gene deletion was associated with decreased replication and cytopathogenicity in p53(+) tumor cells versus matched p53(-) tumor cells, relative to wild-type in RKO and H1299 cells" (page 6653, col 1, ¶ 3). Therefore, the efficacy of the instant adenovirus lies in treatment of p53 (-) tumors. This efficacy has been specifically observed when in combination with chemotherapy (see Kirn et al, page 6666, col 1). As well the specification teaches that this premise is distinctly connected to the replicative condition of the rAd. However, by recitation that the rAd comprises an E1B-55K mutation, the adenovirus to be used in the treatment encompasses a broad and diverse genus of

adenoviruses that need only be linked by a mutation in E1B-55K. The nature of the adenoviruses for treatment of cancer according to the instant invention must be replicative.

Secondly, the method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al (Verma and Somia, Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. Russell teaches "it should first be capable of gaining access to a sufficient number of tumour cells in the patient to bring about a desired therapeutic outcome. Reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle position in a tumour deposit." (page 1165, col 2, ¶ 4-5). In the instant case, the method of delivery of an Onyx based virus is problematic, intratumoral injection is the preferred route of administration as it limits the virus to target tissue due to its cytotoxicity Adenoviral vector use for gene therapy is hindered by the transient nature of the transgene expression coupled with host immune responses. Attempts through oncolytic viral therapy to capitalize on the cell-killing or cellular immune response are also thwarted by the humoral immune responses as taught by Verma and Somia; "Unfortunately for gene therapy, most of the human population will probably have antibodies to adenovirus from previous infection with the naturally occurring virus" (Verma and Somia, p 241). And "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less

desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene (p. 4, column 2).

6) **Summary**. The invention recites a method for treatment of cancer using a replicative adenovirus vector. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established protocols and the inability to predict successful administration of the rAd: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

***Response to Argument***

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph for lack of enablement on pages 10-11 of the amendment filed 9/21/06. Applicants argue that the claims have been amended to result in two groupings of claims that overcome the rejection. First, the adenovirus or DNA is administered directly and secondly with chemotherapy.

Applicants' arguments filed 9/21/06 have been fully considered but they are not persuasive. Applicants' claims drawn to use of chemotherapy in treating neoplastic cancer inpatients overcome by the enablement rejection by virtue of the known ability to treat cancer using chemotherapy. However, claims limited to administration of rAd or rAd DNA lack predictability for a variety of reasons outlined above and briefly summarized here. First, by recitation that the adenovirus is any adenovirus that has a single amino acid mutation in E1B, applicants recite a large genus of unconnected rAd. However, the specification teaches that the rAd of the instant invention is oncolytic in neoplastic cells and therefore, use of any E1b mutant is unpredictable for treatment purposes. Secondly, applicants' claims are drawn to administration of DNA or rAd by any means and yet, as set forth above, the state of the art suggests that administration by any means other then direct administration is highly unpredictable. Applicants have exacerbated this by recitation of administration of DNA encoding recombinant adenovirus. The lack of guidance in the art and the specification for means of administering the DNA such that levels of rAd can be achieved to mediate the intended response, the invention is highly unpredictable.

***Conclusion***

Claims 11-13, 24-28 and 34 are allowed.

Claims 14, 16, 17, 29-32, 33, and 35-47 are rejected.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

**Exhibit C**

**Non-final Office action, mailed 9 May 2007**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/669,768 | 09/24/2003 | Yuqiao Shen | ONYX1047-DIV | 8135 |

37499 7590 05/09/2007
ONYX PHARMACEUITICALS, INC.
2100 POWELL STREET
12TH FLOOR
EMERYVILLE, CA 94608

| EXAMINER | |
|---|---|
| MARVICH, MARIA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |
| **MAIL DATE** | **DELIVERY MODE** |
| 05/09/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/669,768 | SHEN ET AL. | |
| | Examiner | Art Unit | |
| | Maria B. Marvich, PhD | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11-13,24-28,33 and 35-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,24,28,33,39 and 40* is/are rejected.

7)☐ Claim(s) *13, 25-27 and 35-38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Upon further review of the instant claims in a patentability conference, it is apparent that the application is not in condition for allowance. As new grounds of rejection are presented in this action that are not necessitated by applicant's amendment of the claims, this action is non-final.

### *Claim Rejections - 35 USC § 112, first paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 12, 24, 28, 33, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of cancer characterized by p53 loss or deficiency by direct administration Onyx 051 and 053 (comprises a single amino acid substitution in amino acid 240 or 260), does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This is a new rejection.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat.

App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention.** The instant invention is drawn to recombinant adenovirus comprising single amino acid mutations in the E1B-55K gene such that binding to p53 is reduced as compared to binding between p53 and wild-type E1B-55K. The invention utilizes disciplines of molecular biology, virology and clinical technology.

2) **Scope of the invention.** Applicants' claims are broadly drawn to treatment using recombinant adenovirus comprising *any single amino acid mutation* in E1B-55K such that binding to p53 is reduced. Applicants' disclosure teaches development of two such mutants in which amino acid 240 and 260 are mutated to generate Onyx 051 and Onyx 053. These mutants are not able to bind to p53. As described in the specification, the method of the instant invention is directed toward treating cancer using the vectors and is based upon oncolytic replication function of the viruses in infected tumor cells.

3) **Number of working examples and guidance.** The instant invention is drawn to single amino acid mutations within E1B-55k that affect binding to p53. Applicants have constructed 26 mutant rAd in which a single amino acid within the E1B-55K coding sequence was mutated (see e.g. page 12, ¶ 4 and table 2). Two of these mutant R240A and H260A lost ability to bind p53 but did not lose late viral function. Furthermore, the cells were tested for oncolytic affect. U20S and Du145 cells were assayed and demonstrated that the two viruses were cytotoxic.

4) **State of Art.** Enormous efforts have been directed toward the development of vectors for cancer treatments. Adenovirus mutants that lack the ability to bind to p53 are replication

deficient in non-replicating, non-neoplastic cells with p53 but in cells deficient in p53, the virus is replicative and oncolytic. Previously, the art has described generation of rAd comprising deletions, substitutions and frame-shifts which inactivate the ability of E1B-55K to bind to p53 efficiently to generate E1B-p53- mutants. For example, ad2 dl1520 (Onyx 015) comprises a frame-shift mutation at nucleotide position 2022 that generates a stop codon 3 amino acids downstream of the AUG codon resulting in deletion of large region of E1B, US patent 5,677,178 describes the generation of rAd lacking E4orf6 and US 6,080,578 teaches construction of Onyx 019, 020 and 021 in which various amounts of internal sequences are deleted. Kirn et al teach that "the role of p53 in replication-selectivity of dl1520 has been difficult to confirm despite extensive *in vitro* experimentation by many groups, E1B-55K gene deletion was associated with decreased replication and cytopathogenicity in p53(+) tumor cells versus matched p53(-) tumor cells, relative to wild-type in RKO and H1299 cells" (page 6653, col 1, ¶ 3). Therefore, the efficacy of the instant adenovirus lies in treatment of p53 (-) tumors. This efficacy has been specifically observed when in combination with chemotherapy (see Kirn et al, page 6666, col 1).

5) **Unpredictability of the art**. The instant invention is unpredictable for treatment of cancer in humans given the broad recitation of a genus of adenovirus for delivery to p53 lacking neoplastic cells wherein the adenovirus have reduced binding to p53. The instant invention is based upon the premise that targeted mutations within E1B-55K result in a virus that is replicative in tumor cells lack p53 while normal cells do not. As well the specification teaches that this premise is distinctly connected to the replicative condition of the rAd. However, by recitation that the rAd comprises a single amino acid mutation in E1B-55K, the adenovirus to be used in the treatment encompasses a broad and diverse genus of adenoviruses that need only be

linked by a mutation in E1B-55K. Rather the nature of the adenoviruses for treatment of cancer according to the instant invention must be replicative. To this end, applicants generated 26 mutants but only two of these mutants are capable of reduced binding to p53. These mutants (Onyx 051 and 053) comprise a single mutation in amino acid 240 and 260.

Hence, applicants have elucidated the unpredictability of any single amino acid to produce the required functional requirements as only two mutants of 26 produced have the recited functional requirements. As well, applicants have not provided the structural requirements of the single amino acid mutants such that one of skill in the art would be able to identify those mutants that have lost the ability to bind efficiently to p53. Hence, the unpredictability of using the claimed invention in gene therapy is accentuated due to the broad and unpredictable nature of the identifying adenovirus with single amino acid mutations in the E1B 55k gene that have lost the ability to bind p53 and furthermore be used to treat cancer.

6) **Summary.** In view of predictability of the art to which the invention pertains: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

***Conclusion***

Claims 11, 12, 24, 28, 33, 39 and 40 are rejected.

Claims 13, 25-27 and 35-38 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The claims are free of the art because the art fails to teach oncolytic adenoviruses that comprise single amino acid mutations at amino acid 240 or 26 (Onyx 053 and 051). Further, as explained above in the rejection made under 35 USC 112, first paragraph, the claims are drawn to the use of products that would result in therapeutic benefit due to ablated binding to p53. Onyx 053 and 051 are oncolytic viruses that exhibited ablated binding to p53 and lead to decreased cell growth in combination with chemotherapy.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1633

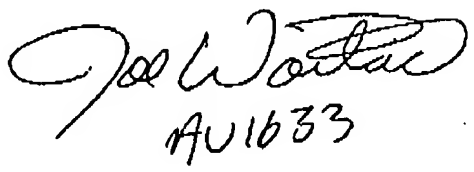

**Exhibit D**

**Published U.S. Patent Application No. US 2005/0053581**